REMARKS

Reconsideration of the Office Action mailed July 22, 2003, (hereinafter "instant Office Action"), entry of the foregoing amendment and withdrawal of the rejection of claims 1-13, 15-25 and 27-29, are respectfully requested. Applicants have enclosed a Notice of Appeal with this Reply.

In the instant Office Action, claims 1-13, 15-25 and 27-29 are listed as pending, and claims 1-13, 15-25 and 27-29 are listed as rejected.

Applicants gratefully acknowledge that the Examiner has withdrawn the rejection of claims 1-13, 15-25 and 27-29 under 35 U.S.C. §102(e) for allegedly being anticipated by Doyle (U.S. Patent no. 6,297,238).

The Examiner has rejected claims 1-13, 15-25 and 27-29 under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for inhibiting vascular hyperpermeability using the compound disclosed on page 33 of the specification, allegedly "does not reasonably provide enablement for all other known and unknown (to be developed in the future) compounds". Applicants respectfully traverse this rejection. Applicants maintain the arguments presented in the Reply filed June 3, 2003.

The Examiner states that he disagrees with Applicants' arguments that the instant claims are directed to identifying a compound that selectively inhibits cellular signally function of KDR and that "Actually, the claims are directed to inhibiting vascular hyperpermeability and therefore, treating various disease states using a specific compound." Indeed, the claims are directed to a method of inhibiting vascular hyperpermeability wherein the method comprises the step of administering a therapeutically effective amount of a compound that inhibits the cellular signaling function of KDR.

The examiner further disagrees with Applicants' assertion that the amount of experimentation required to select compounds that selectively inhibit the cellular signaling function of KDR is routine. The Examiner asserts that "There are unlimited (millions of compounds) compounds available in the prior art and to test each of these compounds in these assays and to find specific compound which selectively inhibits cellular signaling function of KDR and then use this compound to inhibit vascular hyperpermeability in a patient will require undue experimentation". Applicants respectfully disagree. One of ordinary skill in the art, in

seeking compounds to use in the instant invention, would not randomly select compounds for testing. On page 7, lines 13-30, Applicants list numerous patents and published patent applications wherein small molecules that act as tyrosine or serine/threonine kinase inhibitors are identified. Applicants have guided one skilled in the art to these references as a starting point for seeking compounds to use in the instant invention.

One skilled in the art would screen these compounds using the assay provided in the instant application. "Enablement is not precluded by the necessity for some experimentation such as routine screening." *Ansul Co. v. Uniroyal Inc.*, 448 F.2d 872, 878-79, 169 USPQ 750, 762-63 (2d Cir. 1971), cert. denied, 404 U.S. 1018, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972). Further, screening compounds to find those compounds with the desired properties is routine in the art. Using high throughput screening methods it is not only possible but in fact common for medicinal chemists to screen large quantities of compounds.

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 104 (Fed. Cir. 1988) (citing *In re Angstadt,* 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)).

Applicants have not only guided those skilled in the art to patents and published patent applications that disclose compounds with the desired activity, but have also provided assays to use to test these compounds to determine whether they can be used in the instant invention. Thus, Applicants have enabled the instant invention.

Based upon the foregoing, the rejection of claims 1-13, 15-25 and 27-29 under 35 U.S.C. §112, first paragraph, is obviated and should be withdrawn.

The Examiner has rejected claims 1-13, 15-25 and 27-29 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention. The Examiner alleges that the term "a compound that inhibits the cellular signaling function" is indefinite since it is not clear which compound is being referred to. Applicants respectfully traverse this rejection. Applicants maintain the arguments presented in the Reply filed June 3, 2003.

Applicants have defined the compounds of the instant invention by the function of the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases. It is the use of a compound that has the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases that results in the inhibition of vascular hyperpermeability, which is the invention of the instant application. M.P.E.P. 2173.05(g) states:

> A functional limitation is an attempt to define something by what it does, rather than what it is (e.g. as evidenced by its specific structure or specific ingredients). There is nothing inherently wrong with defining some part of an invention in functional terms.

The question of whether compounds can be defined by functional limitations was examined in In re Barr, 444 F.2d 588, 170 USPQ (BNA) 330, (CCPA 1971). In In re Barr, claim 23 read upon a photographic color coupler having the formula COUP-S-R wherein R is an organic radical incapable of forming a dye with said oxidized developing agent and being selected from the group consisting of an alkyl radical, a cycloalkane radical, an aryl radical and a heterocyclic radical containing at least one hetero atom selected from the group consisting of oxygen, sulfur and nitrogen.

The gist of the principal rejection in In re Barr, as expressed by the examiner, is that the claims "appear to read on vast numbers of compounds" and that the Applicants failed "to point out what applicants regard as their invention with the specificity required by 35 U.S.C. 112". Additionally, the examiner held that the phrase "incapable of forming a dye with said oxidized developing agent" is "unduly functional at a point of novelty".

The Board of Appeals affirmed the Examiner's rejection of the claim on the ground that the limitation "incapable of forming a dye with said oxidized developing agent" placed on the organic radical R is "negative and functional". However, the CCPA held:

> that an applicant may invoke the third paragraph of section 112 to justify the specification of one or more elements of a claimed compound in "functional" terms, and that those "functional" terms may be "negative". The real issue in such case is not whether the recital is "functional" or "negative" but whether the recital sets definite boundaries on the patent protection sought – that is, whether those skilled in the relevant art can determine what the claim does or does not read on. Judged by this

> standard, we think it clear that the controverted language complies with the second paragraph of section 112.

Although the phrase in question in In re Barr referred to an organic radical selected from a set of radicals and the phrase in question in the instant application refers to a compound, the issue is essentially the same. Applicants have defined the compound that is used in claims 1-13, 15-25 and 27-29 by a function, namely its ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases. Furthermore, Applicants have provided the assays necessary to test kinase inhibitors to determine whether the claims read on kinase inhibitors with the ability to inhibit the cellular signaling function of KDR without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases. Therefore, Applicants have clearly and definitely defined which compounds these claims read on.

Applicants attach as Exhibit A, a copy of U.S. Patent 6,048,850 ("Young et al."). In this patent, claim 1 is directed to a method for selectively inhibiting PGSH-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment. As in the instant application, this claim is directed to a method of selectively inhibiting a specific activity. As in the instant application, Young et al.'s method comprises administering a compound. However, Young et al. has no examples of compounds which can be used in this method. Young et al. also does not provide any citations to patents, patent applications or other references which disclose suitable compounds. By contrast, in the instant invention Applicants have provided an example of a representative compound as well as citations to patents and applications disclosing kinase inhibitors. Therefore, the rejection is inconsistent with current USPTO practice.

The Examiner alleges that "one has to find a compound from millions and billions of compounds available in the prior art which selectively inhibits cellular signaling function". Applicants respectfully disagree. As argued above in response to the rejection of claims 1-13, 15-25 and 27-29 under 35 U.S.C. §112, first paragraph, Applicants have cited numerous granted patents and published patent applications which disclose compounds that are kinase inhibitors. One of ordinary skill in the art would look to these references as a starting point in seeking compounds for use in the instant invention, thus significantly reducing the number of compounds

to be screened. The Examiner alleges "that there has to be some central core present in the structure of a compound which is critical for this inhibition and therefore, structure of the compound is important to be part of the claim". If one reviews the patents and patent applications cited by the Applicants, one observes that the patents and applications are drawn to different chemotypes. Thus, one cannot say that only one central core is solely responsible for kinase inhibition.

Based upon the foregoing, the rejection of claims 1-13, 15-25 and 27-29 under 35 U.S.C. §112, second paragraph, is obviated and should be withdrawn.

The Examiner has rejected claims 1-13, 15-25 and 27-29 under 35 U.S.C. §102(e) for allegedly being anticipated by Arnold et al. (U.S. Patent no. 6,451,834). The Examiner alleges that Arnold et al. discloses compounds as inhibitors of tyrosine kinase activity having utility for inhibiting vascular hyperpermeability. Applicants respectfully traverse this rejection.

Applicants maintain the arguments presented in the Reply filed June 3, 2003. In that Reply Applicants amended claim 1 to patentably distinguish the instant application from Arnold et al. In the instant application, after entry of the amendments hereinabove, the instant invention is further distinguished from Arnold et al. because it selectively inhibits the cellular signaling function of KDR by disrupting the catalytic kinase response of KDR/VEGFR-2 without significantly affecting the activity of Flt-1/VEGFR-1 or other kinases. Support for this amendment can be found, *inter alia*, on page 8, line 35 to page 9, line 11. As stated on page 9, lines 11-13, due to the selectivity, "This property should afford better toleration to therapy than current therapies or treatment with agents that less selectively disrupt the function of other non-KDR kinases." Therefore, the instant invention offers the advantage of better toleration, that is, fewer side effects, than Arnold et al.

Based upon the foregoing, the rejection of claims 1-13, 15-25 and 27-29 under 35 U.S.C. §102(e) for allegedly being anticipated by Arnold et al. (U.S. Patent no. 6,451,834) is obviated and should be withdrawn.

No fees are due for the instant amendment since the total number of claims after entry of the amendments hereinabove is not more than the total number of claims that Applicants have paid for to date.

Based upon the foregoing, Applicants believe that claims 1-13, 15-25 and 27-29 are in condition for allowance. Prompt and favorable action is earnestly solicited.

If the Examiner believes that a telephone conference would advance the condition of the instant application for allowance, Applicants invite the Examiner to call Applicants' agent at the number noted below.

Respectfully submitted,

Date: October 22, 2003

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